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13-Valent vaccine serotype pneumococcal community acquired pneumonia in adults in high clinical risk groups

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ABSTRACT

There is debate regarding the value of vaccinating adults with the 13-valent pneumococcal conjugate vaccine (PCV-13). This analysis was conducted to investigate the risk of PCV-13 serotype community acquired pneumonia (CAP) in hospitalised adults with co-morbid disease and risk factors for pneumococcal disease in the UK.

Consecutive adults hospitalised (2008–2013) with a primary diagnosis of CAP, were recruited. Pneumococcal aetiology disease was identified by use of pneumococcal urinary antigen detection and serotype identification using a validated multiplex immunoassay or serum latex agglutination. Adults with PCV-13 serotype CAP were compared to those with non-PCV-13 serotype CAP.

Of 2224 patients, PCV-13 serotype CAP was identified in 337 (15.2%) and non-PCV-13 serotype CAP in 250 (11.2%) individuals. Adults aged ≥65 years with one or more clinical risk factors had a significantly lower risk of PCV-13 serotype CAP compared to those aged 16–64 years without clinical risk factors (aOR 0.61, 95%CI 0.41–0.92, p = .018). In a stacked-risk analysis, the presence of incremental clinical risk factors was associated with lower odds of PCV-13 disease (p for trend = .029) Adults with underlying chronic respiratory disease (aOR) 0.56, 95% CI 0.36–0.85, p = .007) and chronic kidney disease (aOR 0.48, 95% CI 0.25–0.92, p = .028) had significantly lower adjusted odds of PCV-13 compared to non-PCV-13 serotype CAP.

This analysis suggests that in the UK, the burden of PCV13 disease is greater in adults outside the traditional 'at-risk' groups compared to adults in 'at-risk' groups.

1. Introduction

Increasing age and the presence of co-morbid diseases are recognised risk factors for pneumococcal disease [1–4]. In addition, pneumococcal attributable mortality is higher in these clinical risk groups [5,6]. Therefore, implementation of appropriate vaccination strategies is important for these individuals. The current UK vaccination policy recommends 23-valent polysaccharide pneumococcal vaccination (PPV-23) in adults at high risk of pneumococcal disease, comprising (a) adults aged between 16 and 64 years with certain co-morbid diseases, and (b) adults aged 65 years and over [7]. However, polysaccharide vaccine effectiveness in these risk groups is debated [8–12]. Immunogenicity studies have shown higher antibody concentrations and functional antibody responses to pneumococcal conjugate compared with polysaccharide vaccination in adults at higher risk of pneumococcal disease including those with human immunodeficiency virus (HIV), chronic obstructive pulmonary disease and older adults [13–15]. Therefore, such patients may benefit from the administration of pneumococcal conjugate vaccination (PCV) in addition to, or in place of the current polysaccharide vaccine. In randomised controlled trials in Malawi and the Netherlands, administration of the pneumococcal conjugate vaccine reduced vaccine-type (VT) invasive pneumococcal disease (IPD) and community acquired pneumonia (CAP) in risk groups of immunocompromised adults with HIV and those over

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the age of 65 years, respectively [16,17]. However, any assessment of the benefits of vaccinating adults with the conjugate vaccine needs to take into account the burden of VT disease in the target group. In the UK, there has been a substantial decrease in adult pneumococcal VT disease as a consequence of herd protection following the introduction of the infant pneumococcal vaccination programme; this decrease is apparent for both invasive and non-invasive pneumococcal disease [18–21]. In patients with IPD, these herd effects appear similar among patients with and without clinical risk factors for pneumococcal disease [3]. There are no such relevant data in adults with non-invasive pneumococcal pneumonia.

In this study, we sought to determine whether hospitalised individuals at high risk of pneumococcal disease are more likely to have PCV-13 serotype CAP compared to non-PCV-13 serotype CAP.

2. Methods

2.1. Study design

We conducted a prospective cohort study of consecutive adult patients admitted, with a primary diagnosis of community acquired pneumonia, to two large university hospitals in Nottingham, between September 2008 and 2013. Combined, these two hospitals cover the catchment area for acute and emergency admissions in the Greater Nottingham area. All patients admitted to medical admissions units were screened every weekday, using radiological and clinical records, to assess for study eligibility. Study eligible patients were aged 16 years or over, presenting with symptoms of a lower respiratory tract infection (at least one of: cough, increasing breathlessness, sputum production and fever), who had radiographic infiltrates consistent with respiratory infection, and who were treated by their clinical team for a diagnosis of CAP. Adults hospitalised in the 10 days preceding the index admission or who had a diagnosis of tuberculosis or post-obstructive pneumonia were excluded. Informed consent was obtained from all study patients; in the event that patients lacked capacity, patient personal consultees were approached for proxy consent. Patient demographics and clinical details were collected from patient records. All study procedures were approved by Nottingham Research Ethics Committee.

2.2. Study population

Routine microbiological investigations were performed at the discretion of the clinical team. In addition, urine samples were taken on admission from each individual for pneumococcal specific microbiological analysis; Binax-NOW® assays were performed for pneumococcal C-polysaccharide urinary antigen detection (UAD) at the local microbiological laboratories whilst the remaining volume of urine was frozen and batch transported to Public Health England (PHE)'s Respiratory and Vaccine Preventable Bacteria Reference Unit in Colindale for serotyping of pneumococcal strains by a multiplex immunoassay (Bio-plex). The Bio-plex assay was validated for detection of pneumococcal serotypes 1, 3, 4, 5, 6A/C, 6B, 7F/A, 8, 9V, 14, 18, 19A, 19F and 23F [22]. The sensitivity and specificity for pneumococcal detection using the Binax-NOW® method, is 74% and 97%, respectively and for the Bio-plex method, is 79% and 99%, respectively [22,23]. Bacteraemic cases of CAP due to *Streptococcus pneumoniae* were identified and serotyped by serum latex agglutination at PHE's reference laboratory. Patients were considered to have pneumococcal CAP if any of the following criteria were met: (a) a positive pneumococcal UAD, or (b) a positive blood culture for *S pneumoniae,* or (c) pneumococcal serotype detection by the Bio-plex assay.

2.3. Statistical considerations

Statistical analyses were performed using Stata/IC 13.1 (©StataCorp., 2013). Serotypes were grouped into PCV-7 types (serotypes 4, 6B, 9V, 14, 18C, 19F and 23F), 'additional' PCV-13 types not present in PCV-7 (serotypes 1, 3, 5, 6A/C, 7F/A, 19A) and 'other' non-PCV-13 serotypes. PCV-13 disease was defined as the identification of one or more of serotypes in either the PCV-7 or 'additional' PCV-13 groups. Non-PCV-13 disease was defined as the isolation of any other pneumococcal serotype or the presence of 'untyped' non-invasive pneumococcal CAP (based on a positive UAD). Baseline characteristics and putative co-morbid disease risk factors for PCV-13 disease were compared using Pearson's chi-square or Fisher's tests for categorical variables, and the Mann Whitney *U* test for non-parametric continuous variables. The independent association between baseline co-morbidity and PCV-13 disease compared to non-PCV-13 disease was examined using a multivariable logistical regression model; those co-morbid diseases with a p value of <0.2 on univariate analysis were included in the multivariable model. Likelihood ratio tests were used to determine the best model fit for continuous variables. Secondary analysis were conducted examining the odds of PCV-13 disease in (a) all 'at-risk' individuals (defined as those aged 16–64 with a clinical risk factor for pneumococcal disease *or* those ≥65 years), (b) individuals stratified according to age (dichotomised at 65 years) and the presence of a clinical risk factor for pneumococcal disease: (1) aged 16–64 years without a clinical risk factor, (2) aged 16–64 years with one or more clinical risk factors, (3) aged ≥65 years without a clinical risk factor, (4) aged ≥65 years with one or more clinical risk factors and (c) individuals with increasing numbers of clinical risk factors; gender was included *a priori* in these models. Clinical risk factors for pneumococcal disease were defined as those eligible for pneumococcal vaccination in the UK as described in PHE's 'Immunisation against Infectious Diseases'; in brief, risk factors included chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, immunosuppression, diabetes, splenic dysfunction and individuals with cerebrospinal fluid (CSF) leaks or cochlear implants [7]. Immunosuppression was defined as the presence of splenic dysfunction, haematological disease including malignancy, solid organ or bone marrow transplant, immunodeficiency, treatment with immunosuppressive medication (not including steroids) or HIV; all other case definitions were derived from a previous study examining clinical risk groups in pneumococcal disease [24].

Incidence data for pneumococcal CAP in the Greater Nottingham area were calculated using data on population demographics collected from (a) the National Infection Service, PHE, for adults aged 16–64 with clinical risk factors, and (b) the UK census (2011) for adults aged ≥65 years [25]. As there is no national registry of risk groups for pneumococcal disease, population demographic data for influenza risk groups were taken as a surrogate measure for incidence calculations [26].

3. Results

3.1. Study population

Over the 5 year study period, 2702 patients were eligible for study inclusion. Of these, 284 (10.5%) were subsequently found to have an alternative diagnosis to CAP and in a further 194 patients, study consent was not obtained. The final study cohort consisted of 2224 adults. Patients in whom consent was not obtained were older (median age: 82 years, IQR 73–89 years versus 71 years, IQR 56–80 years, $p < .001$) and were more likely to have chronic kidney disease (13.4% versus 7.6%, $p = .004$), cerebrovascular

disease (21.8% versus 9.1%, p < .001) and dementia (33.5% versus 2.0%, p < .001) compared to patients in the study cohort. They were also less likely to have chronic respiratory disease (14.4% versus 25.7%, p < .001). No other biases in co-morbid diseases were observed.

Pneumococcal CAP was diagnosed in 643 of 2224 (28.9%) individuals. Urine was unavailable for serotype analysis in 56 (8.7%) of 643 cases. One or more serotypes were identified in 429 (66.7%) of 643 cases of pneumococcal CAP; the remainder represent untyped cases of pneumococcal CAP. Cases where urine was unavailable for serotyping were excluded from analysis of the association of clinical risk group and PCV-13 disease.

3.2. Baseline characteristics

Of 643 patients with pneumococcal CAP, 294 (45.7%) had one or more clinical risk factors for pneumococcal disease; of these, chronic respiratory disease (n = 130, 44.2%) and chronic heart disease (n = 124, 42.2%) represented the majority of cases. There were 68 patients (10.6%) aged 16–64 years with a clinical risk factor and 377 (58.6%) patients were aged ≥65 years. Three hundred and forty-nine (54.3%) patients with pneumococcal disease had no underlying clinical risk factor for pneumococcal disease; one clinical risk factor was present in 205 (31.9%) patients, two clinical risk factors were present in 62 (9.6%) patients and three or more clinical risk factors were present in 27 (4.2%). Diabetes (9.8%) and chronic respiratory disease (8.7%) represented the most common co-morbid diseases amongst patients aged 16–64 years, whilst chronic heart disease (29.2%) and chronic respiratory disease (28.4%) were the most common co-morbid diseases amongst those aged ≥65 years (Table 1). There were no patients with cochlear implants or CSF fluid leaks.

3.3. Clinical risk groups and PCV-13 disease

Of 587 pneumococcal CAP cases where a urine was available for serotype identification, PCV-13 and non-PCV-13 disease comprised 337 (57.4%) and 250 (42.6%) cases respectively. Baseline characteristics of patients with PCV-13 and non-PCV-13 serotype CAP are shown in (Table 2). Patients with underlying chronic respiratory disease and chronic kidney disease had significantly lower odds of PCV-13 disease compared to non-PCV-13 disease (adjusted Odds Ratio (aOR) 0.56, 95% CI 0.36–0.85, p = .007, and aOR 0.48, 95%CI 0.25–0.92, p = .028, respectively). Conversely, those with dementia had significantly higher odds of PCV-13 disease (aOR 3.91, 95%CI 1.10–13.91, p = .036).

Of patients with pneumococcal CAP, 184 (31.4%) were aged 16–64 years with no clinical risk factors, 57 (9.7%) were aged 16–64 years with one or more clinical risk factors, 133 (22.7%) were aged ≥65 years with no clinical risk factors and 213 (36.3%) were aged ≥65 years with one or more clinical risk factors. In the gender-adjusted model, patients aged ≥65 years with one or more clinical risk factors had a significantly lower risk of PCV-13 serotype CAP compared to those aged 16–64 years without clinical risk factors (aOR 0.61, 95%CI 0.41–0.92, p = .018) (Table 3). In a stacked-risk analysis adjusted for gender and age, the presence of incremental clinical risk factors was associated with lower odds of PCV-13 disease (Fig. 1). The gender-adjusted odds of PCV-13 disease was lower in patients that comprised the total 'at-risk' group (those aged 16–64 years with clinical risk factors or those aged ≥65 years): aOR 0.71, 95%CI 0.49–1.02, p = .062.

Table 1
Distribution of co-morbid diseases in adults with pneumococcal CAP.

	16–64 years n = 266	≥65 years n = 377
Chronic heart disease	14 (5.3)	110 (29.2)
Chronic respiratory disease	23 (8.7)	107 (28.4)
Diabetes	26 (9.8)	56 (14.9)
Chronic kidney disease	4 (1.5)	44 (11.7)
Chronic liver disease	6 (2.3)	4 (1.1)
Immunosuppressed	8 (3.0)	10 (2.7)
Cancer	12 (4.5)	26 (6.9)
Dementia	0 (0.0)	19 (5.0)
Cerebrovascular disease	5 (1.9)	62 (16.5)

All values given as n (%).

3.4. Serotype distribution of pneumococcal CAP by risk group

Table 4 shows the distribution of single serotypes with >10 isolates. Serotypes 7F/A and 8 were the most common, both being isolated in 69 patients. Using serotype 8 as reference, serotypes 3, 5 and 14 were significantly associated with causing disease in 'at-risk' patients compared to those not at-risk whilst serotype 7F/A was associated with lower odds of disease in 'at-risk' patients.

3.5. Incidence of pneumococcal CAP in clinical risk groups

The overall incidence of pneumococcal CAP was 20.7 per 100,000 persons whilst that of PCV-13 CAP was 10.8 per 100,000 and non-PCV-13 CAP was 8.0 per 100,000. The highest overall incidence of pneumococcal CAP was observed in those over 65 years (64.3 per 100,00); in these patients the incidence of PCV-13 serotype CAP was 32.9 per 100,000 persons, and that of non-PCV-13 serotype CAP was 26.1per 100,000 persons. The incidence of PCV-13 and non-PCV-13 pneumococcal CAP by clinical risk group is shown in Fig. 2. Incidence rates of non-PCV-13 serotype CAP was two to three fold that of PCV-13 serotype CAP in patients aged 16–64 years with chronic liver disease and those who were immunocompromised. Conversely, patients aged 16–64 years with diabetes had a higher incidence of PCV-13 compared to non-PCV-13 serotype CAP (16.7 versus 5.6, per 100,000 persons).

3.6. Mortality

Overall, 30-day mortality in patients with pneumococcal CAP was 7.5%. Of those individuals 'at-risk' of pneumococcal disease, 30-day pneumococcal CAP mortality was 10.3% compared to 1.0% in those under 65 years considered not at risk. The highest pneumococcal CAP mortality was observed in individuals ≥65 years with a clinical risk factor (14.2%), followed by those ≥65 years without a clinical risk factor (8.6%). For those under 65 years with a clinical risk factor, 30-day mortality was 1.5%. There was no significant difference in 30-day mortality in all individuals with PCV-13 compared to non-PCV-13 serotype CAP (8.3% vs 7.6%; OR 1.10, 95% CI 0.60–2.02, p = .755), nor in those individuals classified as 'at-risk' (11.7% vs 10.5%; OR 1.13, 95% CI 0.60–2.12, p = .701).

4. Discussion

In adults hospitalised with pneumococcal CAP, we found that PCV-13 serotype CAP was 44% less likely in patients with chronic respiratory disease and 52% less likely in chronic kidney disease compared to non-PCV-13 serotype CAP. The odds of PCV-13 serotype CAP were significantly lower with increasing numbers of clinical risk factors for pneumococcal infection.

These results are consistent with findings observed from studies in adult IPD, where PCV-13 serotypes have been shown to be less frequently associated with the presence of underlying co-morbid disease, compared to non-PCV-13 serotypes [5,27,28]. Similarly, a 16-year cohort study demonstrated that individuals with chronic

Table 2
Clinical features of adults admitted with CAP and comparative analysis of those with PCV-13 versus non-PCV-13 serotype CAP.

	All cause CAP	Pneumococcal CAP		OR (95%CI)	p value
	(n = 2224)	Non-PCV-13 disease (n = 250)	PCV-13 disease (n = 337)		
Age					
16–49 years	431 (19.4)	86 (25.5)	58 (23.2)	Reference	.216[a]
50–64 years	424 (19.1)	58 (17.2)	39 (15.6)	1.00 (0.59–1.70)	
65–74 years	468 (21.0)	75 (22.3)	44 (17.6)	1.15 (0.70–1.90)	
75–84 years	577 (25.9)	67 (19.9)	72 (28.8)	0.63 (0.39–1.01)	
≥85 years	324 (14.6)	51 (15.1)	37 (14.8)	0.93 (0.54–1.59)	
Male	1225 (55.1)	180 (53.4)	115 (46.0)	1.35 (0.97–1.87)	.076
Care home resident[b]	92 (4.2)	15 (4.5)	13 (5.2)	0.86 (0.40–1.85)	.702
PPV23 vaccination[b]	931 (47.3)	123 (41.6)	108 (50.2)	0.70 (0.49–1.00)	.052
Smoking status[b]					
Never	612 (29.1)	82 (25.8)	64 (27.2)	Reference	.864[a]
Ex	989 (46.9)	144 (45.3)	97 (41.3)	1.16 (0.76–1.76)	
Current	506 (24.0)	92 (28.9)	74 (31.5)	0.97 (0.62–1.52)	
Alcohol excess	47 (2.1)	9 (2.7)	7 (2.8)	0.95 (0.35–2.60)	.924
Chronic respiratory disease	572 (25.7)	52 (15.4)	66 (26.4)	0.51 (0.34–0.77)	**.001**
Asthma	267 (12.0)	40 (11.9)	39 (15.6)	0.73 (0.45–1.17)	.191
COPD	509 (22.9)	46 (13.7)	60 (24.0)	0.50 (0.33–0.77)	**.001**
Chronic heart disease	500 (22.5)	63 (18.7)	53 (21.2)	0.85 (0.57–1.29)	.451
CCF	146 (6.6)	19 (5.6)	15 (6.0)	0.94 (0.47–1.88)	.853
IHD	249 (11.2)	28 (8.3)	27 (10.8)	0.75 (0.43–1.31)	.306
Diabetes	305 (13.7)	48 (14.2)	26 (10.4)	1.43 (0.86–2.38)	.166
Chronic liver disease	24 (1.1)	5 (1.5)	5 (2.0)	0.74 (0.21–2.58)	.751
Chronic kidney disease	169 (7.6)	17 (5.0)	27 (10.8)	0.44 (0.23–0.83)	**.009**
Immunocompromised	82 (3.7)	6 (1.8)	8 (3.2)	0.55 (0.19–1.60)	.265
Severely immunocompromised[c]	22 (1.0)	0 (0.0)	5 (2.0)	–	–
Active malignancy	169 (7.6)	21 (6.2)	13 (5.2)	1.21 (0.59–2.47)	.597
Dementia	45 (2.0)	16 (4.8)	3 (1.2)	4.10 (1.17–14.34)	**.016**
Cerebrovascular disease	202 (9.1)	42 (12.5)	23 (9.2)	1.41 (0.82–2.41)	.213
Number of clinical risk factors:					
0	1078 (48.5)	198 (58.8)	119 (47.6)	Reference	.016[a]
1	751 (33.8)	98 (29.1)	92 (36.8)	0.64 (0.44–0.92)	
2	289 (13.0)	30 (8.9)	26 (10.4)	0.69 (0.39–1.23)	
≥3	106 (4.8)	11 (3.3)	13 (5.2)	0.51 (0.22–1.18)	
Low severity (CURB65 ≤ 1)	1029 (46.3)	134 (39.8)	100 (40.0)	Reference	.732[a]
Moderate severity (CURB65 = 2)	684 (30.8)	107 (31.8)	84 (33.6)	0.95 (0.65–1.40)	
High severity (CURB65 ≥ 3)	511 (23.0)	96 (28.5)	66 (26.4)	1.09 (0.72–1.63)	
30-day mortality	230 (10.3)	28 (8.3)	19 (7.6)	1.10 (0.60–2.02)	.755

All values expressed as n (%);
PPV23 – 23-valent pneumococcal polysaccharide vaccine ([b] data unavailable for 254 patients), COPD – chronic obstructive pulmonary disease, CCF – congestive cardiac failure, IHD – ischaemic heart disease.
OR and p values compare PCV-13 serotype disease to non-PCV-13 disease.
Bold values indicate p < 0.05.
[a] – p for trend;
[b] – Care home and smoking status unavailable for 26 and 117 patients, respectively.
[c] – Severely immunocompromised group consists of bone marrow transplant patients, patients with acute and chronic leukaemia, multiple myeloma or those with genetic disorders affecting the immune system.

Table 3
Association between clinical risk group and PCV-13 disease.

	aOR (95% CI)	p value
16–64 yrs with no clinical risk factor	Reference	–
16–64 yrs with clinical risk factor(s)	0.58 (0.32–1.06)	.077
≥65 yrs with no clinical risk factor	0.98 (0.61–1.55)	.915
≥65 yrs with clinical risk factor(s)	0.61 (0.41–0.92)	**.018**
Male gender	1.43 (1.02–1.99)	**.037**

Bold values indicate p < 0.05.

respiratory disease and chronic kidney disease were more likely to have non-vaccine type (NVT) (non-PCV-13 and non-PPV-23) IPD compared to PCV-13 disease [28]. However, in contrast to analyses in IPD cohorts which have shown an association with younger age and PCV-13 serotype disease, we observed no association between PCV-13 serotype disease and age [5,28].

In the UK, introduction of the infant vaccination programme has been highly successful in reducing VT serotype IPD as a consequence of herd protection [18,29,30]. Whether these reductions in VT disease equally apply to adults at clinical risk of pneumococcal disease as to other adults is less well defined [3,31,32,33]. In addition, despite overall decreases in VT pneumococcal disease, increases in NVT IPD have been observed in at risk populations including the immunocompromised and those over 65 years [20,28,34]. Our findings, involving mainly adults with non-invasive CAP, adds to the evidence base that older adults with clinical risk factors are more likely to have non-PCV-13 serotype CAP compared to PCV-13 serotype CAP. Differences in the invasive potential of pneumococcal serotypes may provide a possible explanation for these observations; non-PCV-13 serotypes are generally less invasive compared to PCV-13 serotypes [27]. Consequently, non-PCV-13 serotypes may be more likely to act as opportunistic pathogens in older patients with co-morbid diseases [35–38].

Our finding that patients with dementia were much more likely to be hospitalised with CAP due to PCV-13 serotypes was dominated by patients with dementia who had PCV-7 serotype disease (11 of 19 patients) identified in the first 2 years of the study. Whilst

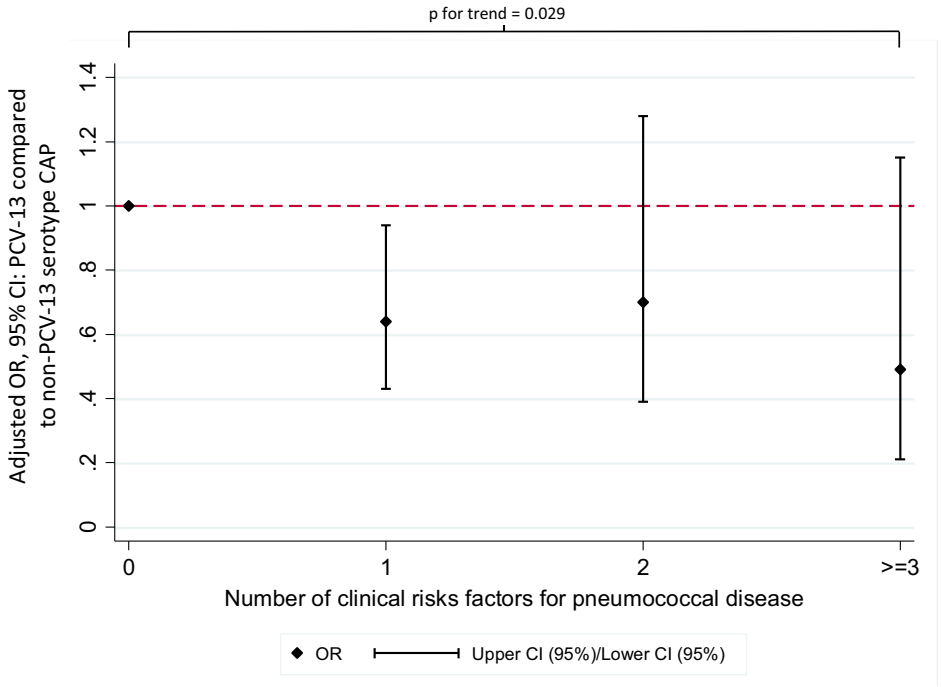

Fig. 1. Gender and age adjusted odds of PCV-13 serotype CAP with increasing numbers of clinical risk factors for pneumococcal infection.

Table 4
Association between pneumococcal serotypes and individuals at risk of pneumococcal disease.

Serotype	'At-risk' group (n = 403)	No risk group (n = 184)	OR (95%CI)	p value
1	34	28	0.78 (0.39–1.57)	.485
3	21	3	4.50 (1.22–16.56)	**.024**
4	9	7	0.83 (0.28–2.48)	.734
5	20	4	3.21 (0.99–10.43)	**.052**
6A/C	19	4	3.05 (0.94–9.95)	.064
7F/A	25	44	0.37 (0.18–0.73)	**.004**
8	42	27	Reference	
14	41	9	2.93 (1.23–6.98)	**.015**
19A	27	11	1.58 (0.67–3.70)	.294

All values given as n; 'At-risk' group defined as those aged 16–64 years with clinical risk factors for pneumococcal disease *or* those aged ≥65 years.
Bold values indicate $p < 0.05$.

social isolation and lack of child contact in patients with dementia might explain this finding, confirmation of this association in a different patient cohort is necessary [39].

In adults under 65 years, the presence of chronic liver disease or immunocompromise were associated with the highest incidence of pneumococcal CAP. Van Hoek et al. linked UK IPD cases to Hospital Episode Statistics (HES) data to estimate incidence rates for clinical risk groups; they too demonstrated that the highest incidence of pneumococcal disease in this age group occurred in these conditions [3]. The absolute incidence rates for each clinical risk factor were considerably lower in our study compared to that of Van Hoek et al. and two similar population based IPD studies conducted in Finland and the Netherlands [3,6,26]. Possible reasons for this difference include (a) the inclusion of infants and children in previous IPD studies and (b) incomplete recruitment of adults in certain high risk groups, to the current study.

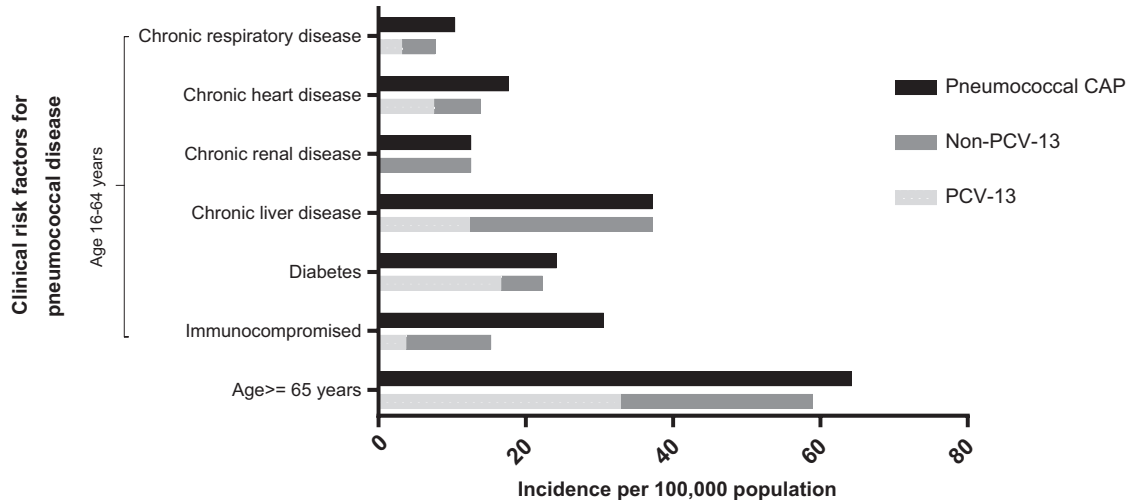

Fig. 2. Incidence of PCV-13 and non-PCV-13 pneumococcal CAP by age and clinical risk group.

4.1. Strengths and limitations of this analysis

To our knowledge this is the first report to describe the relationship between clinical risk factors for pneumococcal disease and PCV-13 serotype CAP in adults. A key strength of this study is the identification of pneumococcal serotypes in non-bacteraemic cases of CAP. The main limitation of the study was the inability to detect non-PCV-13 serotypes other than serotype 8 in patients with non-bacteraemic CAP. For the comparative analysis, patients with untyped pneumococcal CAP were considered to have non-PCV-13 serotype CAP. Although the Bio-plex assay has a high sensitivity for the detection of 14 serotypes, some patients with untyped pneumococcal CAP may have had PCV-13 serotype CAP; thus any differences identified between groups are likely to be conservative for the association with PCV-13 serotype disease. The overall proportion of study patients with dementia as a co-morbid illness was low in this study. Whilst this may be a true finding, we are unable to exclude temporal selection bias given the high prevalence of PCV-7 serotypes and contemporaneous national data from the British Thoracic Society CAP audit which demonstrated an increase in the proportions of patients with dementia over the study period (the inverse of which was seen in the present study) [40].

For incidence calculations, population level data on influenza risk groups from 2015/16 were used in place of pneumococcal clinical risk groups as a national registry of the latter is lacking. Influenza risk groups overlap with pneumococcal clinical risk groups, with the exception of cochlear implants and CSF leaks, the latter two of which had no study patients. The impact of this limitation on study results is likely to be small. Completeness of case ascertainment and microbiological testing would also be expected to influence incidence calculations. A small proportion of patients admitted over weekends and with very short lengths of stay may not have been recruited to the study; urine samples were also not available for serotype analysis in 56 (8.7%) patients with pneumococcal CAP. Therefore, incidence rate estimates are likely to be conservative.

4.2. Implications of results

Whilst PCV-13 vaccine efficacy against VT serotype pneumococcal pneumonia has been demonstrated in older adults, the effect of conjugate vaccine administration across other clinical risk groups remains uncertain [17]. An important question for pneumococcal vaccine policy is whether there are identifiable groups of adults at risk of VT disease despite herd protection effects arising from pneumococcal vaccination programmes. We found that in the presence of a strong infant pneumococcal vaccination programme, the burden of PCV13 disease is greater in adults outside the traditional 'at-risk' groups compared to adults in 'at-risk' groups. Adults in the traditional 'at-risk' groups were more likely to be hospitalised with non-PCV-13 serotype CAP than PCV-13 serotype CAP. Offering PCV-13 vaccination to adults in clinical risk groups may therefore be of limited benefit in this setting.

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Author contributions

Study conception and design: PD, CT and WSL.
Acquisition of data: CR, TB, SG and CS.
Analysis and interpretation of data: PD, CT, TM and WSL.
Drafting of manuscript: PD and WSL.
Critical revision: all authors.

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Conflict of interest

PD – received salaries derived from an investigator initiated unrestricted grant from Pfizer.

CR – received salaries part funded by an NIHR grant and an investigator initiated unrestricted grant from Pfizer during his research.

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